PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

see form PCT/ISA/220

response: 13.9.05 + 3m = 13.12.05
06.10.03 + 22m = 06.08.05

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing (day/month/year) 13/9/2005
see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220 R3074-PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/BE2004/000142	06.10.2004	06.10.2003

International Patent Classification (IPC) or both national classification and IPC
G01N31/00, A01N43/00, A61K31/70, C07H21/02, C07H21/04, C07H21/00

Applicant
UNIVERSITEIT GENT

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/BE2004/000142

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20-35

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 20-35

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-19, 36, 37

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19,36,37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-7,11-12,14,37
	No:	Claims	8-10,13,15-19,36
Industrial applicability (IA)	Yes:	Claims	1-19,37
	No:	Claims	36 (no opinion)

2. Citations and explanations

   see separate sheet

1. Regarding Part IV, Non-unity; Art.17(3)(a) PCT; Rule 13(1) PCT; Rule 40 PCT:

1) The present application does not comply with the requirements of unity of invention. 2 (TWO) separate inventions have been identified. Each of them is characterised by an individual "special technical feature"; there is no technical interrelation between these inventions (see below). The applicants are therefore asked to pay additional search fees. The International Search Report will otherwise be limited to the first invention specified above [Art. 17(3)(a) PCT; Rule 13(1) PCT; Rule 40 PCT].

2) The following arguments reflect the preliminary opinion of the ISA concerning unity of invention:

2.1. Rule 13(2) PCT demands that "Rule 13.1 PCT shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression 'special technical features' shall mean those technical features which define a contribution which each of the claimed invention considered as a whole makes over the prior art."

The PCT Preliminary Examination Guidelines C-III 7.6 state more precisely that "if the common matter of the independent claim is well known, and the remaining subject-matter differs without there being any unifying novel concept common to all of them, then clearly there is lack of unity".

2.2. The presently claimed subject-matter does not fulfill the necessary requirements on unity of invention as outlined above:

2.3. In view of the disclosure of the present application, the technical problem to be solved is the following: "to the more efficient modulation of a target gene using antisense oligomers" (page 3, lines 15-16), in particular IL-1R1(pp. following).

The alleged common technical feature of all solutions to this problem is the following:

"exon bridging probes, which are targeted to the spliced mRNA and not to pre-spliced mRNA, which bridge sequences in the mature mRNA which encompass the junction of two consecutive exons obtained after the removal by splicing of at least one intron between two exons from the primary pre-spliced RNA transcript" (page 3, lines 16-21).

2.4. Prior art DeMoor et al. (1998) Experimental Cell Research 243: 11-21 XP002923758, discloses a proposed solution to the said technical problem, Fig. 1A and elsewhere (antisense oligonucleotide bridging exon junction 1,2 of the mature TS mRNA.

Moreover, the inhibition of IL-1R1 receptor expression and therefore activity using various antisense oligos has previously been documented (see for example, Miraglia et al. (1996) Int. J. immunopharmac. 18: 227-240; US patent 5,856,099; Burch et al. (1991) J. Clinic. Invest. 88: 1190-1196). The skilled person would reasonably contemplate applying the modulation of gene target expression by the use of exon-boundary bridging oligos in the context of the expression inhibition of IL-1R1 given the information in DeMoor et al. supra. This is particularly relevant in the context of claim 25.

2.5. It follows that there is no common special technical feature for the whole scope of the present application that would define an appreciable contribution (e.g. novel and/or non-trivial) over the prior art.

2.6. In view of the prior art (supra), the technical content of the present application has to be rearranged into 2 individual objective problems with independent solutions (non-unity a posteriori):

- Problem 1: The provision of a method for the increase in extracellular matrix compounds in a cell population.
- Solution 1: The inhibition of IL-1R1 expression using an exon-bridging antisense oligo.

- Problem 2: The provision of a method for the modulation of the expression of a target gene in a cell population.
- Solution 2: The inhibition of mature mRNA function by the use of an exon-bridging antisense oligo directed against the mature mRNA.

2.7 Please be advised that disclaimers may restore novelty, but not an inventive step and a common inventive concept.
3) Please note also that Rule 13 PCT has a regulatory function (to prevent unjustified saving of fees, and to ensure ready comprehensibility). Also from this more pragmatic approach the present application lacks unity of invention:
First, due to the lack of constant characteristic "special technical features", competitors cannot inform themselves readily on the existing situation regarding protective rights.
Second, the equitable levying of fees has to be respected. Because of its heterogeneous content, the present application entails a far greater than average expense in the procedure up to grant (keep in mind that there is an ample background concerning subject-matter with related technical and functional features, thus necessitating several independent searches of restricted scope).

2. Regarding Part V; Art. 33 PCT:

a. Claims 8-10, 13, 15,16,19 and 36 are not considered to involve an inventive step

under Art. 33(1)(3) PCT.

b. The closest prior art to claim 8 is US-A-5 856 099 (MIRAGLIA ET AL) 5 January 1999 (1999-01-05), which discloses antisense oligonculeotides which in suitable pharmaceutical compositions are said to be useful in the treatment of diseases amenable to treatment through the modulation of The Type I interleukin-1 receptor (IL-1R1). Modulation suggested is the inhibition of the expression of the gene using antisense oligos directed to various regions of the relevant coding mRNA. Table 1 in column 11 shows that the antisense compositions include seq. ID Nos: 13-16, which are directed to the splice junctions of exons 1, 2 and 3, respectively. The examples show that these have an inhibitory effect on the expression of IL-1R1.

The claim 8 generic antisense oligo differs in that it is defined as being "exon-bridging", in other words as bridging the junction between exons. The objective technical problem is therefore seen to be the provision of further antisense oligomers capable of inhibiting the expression of IL-1R1 receptor.

This problem is self-evident from this cited art and from that remaining.

The solution is not considered to involve an inventive step, since it has been proposed in the inhibition of TS mRNA translation, in DEMOOR J M ET AL: "ANTISENSE NUCLEIC ACIDS TARGETED TO THE THYMIDYLATE SYNTHASE (TS) MRNA TRANSLATION START SITE STIMULATE TS GENE TRANSCRIPTION" EXPERIMENTAL CELL RESEARCH, SAN DIEGO, CA, US, vol. 243, 1998, pages 11-21, XP002923758 ISSN: 0014-4827; (see in particular Fig. 1A on page 12). The concept of using oligos spanning the exon-exon boundary would therefore be known to the skilled person. It would therefore be logical for the skilled person to apply this knowledge in the field of inhibition of IL-1R1 expression, given that the inhibition of both TS and IL-1R1 expression have therapeutic implications. An inventive step is therefore not accorded to the subject-matter of claim 8 and, mutatis mutandis to claims 15, 16, 36 and 19, the latter of which lists a whole range of disorders where IL-1R1 expression may or may not be implicated. Note that since the inhibition of IL-1R1 expressiob by antisense has been recommended as a treatment for, inter alia, arthritis, which is characteriased by a cartilage or osteochondrial defect, claims 17 and 18 do not have an inventive step for the same reasons.

Moreover, this also appears to apply to the general features of claim 10, dependent on claim 8, and to claims 9, and 13 which specify generic oligos bridging exons 02-03 and 05-06, respectively, of the mature mRNA. These embodiments appear to represent logical choices, available to the skilled person available at the time from the knowledge about exon-exon junctions in IL-1R1 mRNA, and which do not, per se

appear to provide any unforseen advantages and/or surprising effects over the prior art inhibitory oligomers.

The specific oligomers of claims 11, 12 and 14 do, however, show the advantages over the art 3' inhibitory oligomer of US 5,856,099 since it would appear that a lower dosage is required in order to provide an inhibition of IL-1R1 expression (Example 6, pages 37-38 of the application). This might form the basis of an inventive step.

c. The remaining claimed subject-matter is also considered to involve an inventive step.

There is no characterisation in the art for in vitro methods of increasing the extracellular matrix synthesis of a cell population by employing antisense inhibition of IL-1R1. It is not conceivable, therefore that the skilled person would combine the features of exon-bridging antisense oligomers with the inhibition of IL-1R1 to arrive at the method of claim 1. This also applies to the subject-matter of claim 37.

3. The International Examining Authority reserves its opinion on industrial activity under Art. 33(1)(4) PCT regarding claim 36, directed to a method of treatment of the human or animal body. There are no common, unified guidelines for the assessment of such a claim within the PCT system.

4. Regarding Part VIII, Art. 6, claim 19 is directed to the use of antisense oligomers for the preparation of a medicament for the treatment of a whole range of diseases, where the use of oligomers are not supported by any experimental teaching in the application and would also not appear to provide solutions to many of the disease states mentioned This leads to a deficiency in teaching under Art. 5 PCT, since the skilled person would not be able to apply sufficient knowledge in order to carry out the claimed solutions.